Journal Pre-proof

Lung response to a higher positive end-expiratory pressure in mechanically ventilated patients with COVID-19

Alessandro Protti, M.D., Alessandro Santini, M.D., Francesca Pennati, Ph.D., Chiara Chiurazzi, M.D., Massimo Cressoni, M.D., Michele Ferrari, M.D., Giacomo E. Iapichino, M.D., Luca Carenzo, M.D., Ezio Lanza, M.D., Giorgio Picardo, M.D., Pietro Caironi, M.D., Andrea Aliverti, Ph.D., Maurizio Cecconi, M.D.

PII: S0012-3692(21)04100-3

DOI: https://doi.org/10.1016/j.chest.2021.10.012

Reference: CHEST 4660

To appear in: *CHEST*

Received Date: 3 July 2021

Revised Date: 25 September 2021

Accepted Date: 6 October 2021

Please cite this article as: Protti A, Santini A, Pennati F, Chiurazzi C, Cressoni M, Ferrari M, Iapichino GE, Carenzo L, Lanza E, Picardo G, Caironi P, Aliverti A, Cecconi M, Lung response to a higher positive end-expiratory pressure in mechanically ventilated patients with COVID-19, *CHEST* (2021), doi: https://doi.org/10.1016/j.chest.2021.10.012.

Word count text: 2973/3200

Word count abstract: 287/300

Lung response to a higher positive end-expiratory pressure in mechanically ventilated patients with COVID-19

Short title: Lung response to PEEP in COVID-19

Alessandro Protti, M.D. [1, 2]; Alessandro Santini, M.D. [2]; Francesca Pennati, Ph.D. [3]; Chiara Chiurazzi, M.D. [2]; Massimo Cressoni, M.D. [4]; Michele Ferrari, M.D. [2]; Giacomo E. Iapichino, M.D. [2]; Luca Carenzo, M.D. [2]; Ezio Lanza, M.D. [5]; Giorgio Picardo, M.D. [1]; Pietro Caironi, M.D. [6, 7]; Andrea Aliverti, Ph.D. [3]; Maurizio Cecconi, M.D. [1, 2]

1) Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
2) Department of Anesthesia and Intensive Care Units, Humanitas Clinical and Research Center – IRCCS, Rozzano, Milan, Italy
3) Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy
4) Unit of Radiology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy

5) Department of Radiology, Humanitas Clinical and Research Center – IRCCS, Rozzano, Milan, Italy
6) Department of Oncology, University of Turin, Turin, Italy
7) Department of Anesthesia and Critical Care, Azienda Ospedaliero-Universitaria S. Luigi Gonzaga, Orbassano, Italy

Corresponding author: Alessandro Protti, Department of Anesthesia and Intensive Care Units, Humanitas Clinical and Research Center – IRCCS, Rozzano (Milan), Italy. Phone number:+39.02.82244135. E-mail address: alessandro.protti@hunimed.eu

Conflicts of interests: the authors declare no competing interests.

Funding statement: support was provided solely from institutional and/or departmental sources.

Prior Presentations: none.

Keywords: mechanical ventilation; acute respiratory distress syndrome; positive end-expiratory pressure; coronavirus disease 2019

Abstract

Background

International guidelines suggest using a higher (>10 cmH_2O) positive end-expiratory pressure (PEEP) in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) due to the novel coronavirus disease (COVID-19). However, even if oxygenation generally improves with a higher PEEP, compliance and arterial carbon dioxide tension ($PaCO_2$) frequently do not, as if recruitment was small.

Research question

Is the potential for lung recruitment small in patients with early ARDS due to COVID-19?

Study design and methods

Forty patients with ARDS due to COVID-19 were studied in the supine position within three days of endotracheal intubation. They all underwent a PEEP trial, where oxygenation, compliance, and $PaCO_2$ were measured with 5, 10, and 15 cmH_2O of PEEP and all other ventilatory settings unchanged. Twenty underwent a whole-lung static computed tomography at 5 and 45 cmH_2O, and the other twenty at 5 and 15 cmH_2O of airway pressure. Recruitment and hyperinflation were defined as a decrease in the volume of the non-aerated (density above -100 HU) and an increase in the volume of the over-aerated (density below -900 HU) lung compartments, respectively.

Results

From 5 to 15 cmH_2O, oxygenation improved in thirty-six (90%) patients but compliance only in eleven (28%) and $PaCO_2$ only in fourteen (35%). From 5 to 45 cmH_2O, recruitment was 351 (161-462) ml and hyperinflation 465 (220-681) ml. From 5 to 15

cmH_2O, recruitment was 168 (110-202) ml and hyperinflation 121 (63-270) ml. Hyperinflation variably developed in all patients and exceeded recruitment in more than half of them.

Interpretation

Patients with early ARDS due to COVID-19, ventilated in the supine position, present with a large potential for lung recruitment. Even so, their compliance and $PaCO_2$ do not generally improve with a higher PEEP, possibly due to hyperinflation.

Acute respiratory distress syndrome (ARDS) is characterized by inflammatory pulmonary edema with heavy lungs, acute hypoxemia, and low compliance.[1] Computed tomography (CT) has clarified that hypoxemia depends on a large number of alveoli perfused but not aerated and low compliance on the small dimension of the ventilated lung.[2] A higher positive end-expiratory pressure (PEEP) can be used to reopen the non-aerated alveoli (anatomical recruitment) and relieve hypoxemia.[3,4] As ventilation gets distributed in more units, compliance will probably increase, and the arterial carbon dioxide tension ($PaCO_2$) will probably decrease.[4-6] However, in patients with a small non-aerated compartment, recruitment is modest or nil. With a higher PEEP, oxygenation can still improve via other mechanisms, including a decrease in the cardiac output,[6,7] but compliance and $PaCO_2$ will probably not, because of alveolar overdistention.[4-6] As a general rule, the more severe the hypoxemia, the larger the alveolar collapse, the greater the probability of a positive effect of a higher PEEP on lung morphology (i.e., larger recruitment), lung function (i.e., better gas exchange and mechanics),[4] and possibly survival.[8,9]

In line with this general model and recommendations for treating ARDS of other origins,[10] international guidelines suggest using a higher PEEP (>10 cmH_2O) for moderate-to-severe hypoxemia due to COVID-19.[11] However, many patients with this novel disease present with less than expected alveolar collapse,[12,13] so that their potential for recruitment may be smaller than in other ARDS. Accordingly, compliance or $PaCO_2$ frequently worsen with a higher PEEP.[13-20] These, and other data,[21-23] suggest that in COVID-19, hypoxemia is not only due to alveolar collapse and that the primary response to a higher PEEP is not always lung recruitment.

This study aimed to describe the response to a higher PEEP in patients with early ARDS due to COVID-19. We hypothesized that this is generally negative because the potential for lung recruitment is low.

Methods

This study was approved by our institutional review board (protocol 465/20). Informed consent was obtained according to local regulations.

Forty patients with laboratory-confirmed COVID-19 underwent a PEEP trial and a lung CT within three days of endotracheal intubation. Inclusion criteria were: (i) admission to our intensive care unit (ICU) with ARDS;[24] (ii) ongoing invasive mechanical ventilation with deep sedation and paralysis; and (iii) one of the authors available for collecting data. Exclusion criteria were: (i) lung CT already taken after intubation; (ii) patient too unstable for transfer to the radiology unit; and (iii) pulmonary air leak. We studied ten non-consecutive patients from 1/3/2020 to 31/5/2020, when we were frequently unavailable due to the exceptional clinical workload, and thirty consecutive ones from 16/10/2020 to 9/12/2020 (Figure E1). Those with a body mass index >35 Kg/m^2 (obese) underwent a slightly different protocol than the others (see below).

PEEP trial

Patients were studied in the supine semi-recumbent position. Following a recruitment maneuver,[4] PEEP was set at 15, 10, and 5 cmH_2O. If the patient was obese, PEEP was set at 20, 15, and 10 cmH_2O. Other settings were kept constant. Gas exchange and respiratory system mechanics were assessed after twenty minutes at each PEEP level.

Lung CT

Patients were studied in the supine horizontal position. Following a recruitment maneuver,[4] a lung CT was taken at 45 and 5 cmH_2O (the first twenty patients) or 15 and 5 cmH_2O (the other twenty patients) of airway pressure. If the patient was obese, CTs were taken at 45 and 10 or 20 and 10 cmH_2O. The total (tissue and gas) volume, the tissue weight, and the gas volume of the whole lung and its non-aerated (density above -100 HU), poorly-aerated (from -100 to -500 HU), normally-aerated (from -500 to -900 HU), and over-aerated (below -900 HU) compartments were measured as in references 2 and 4. The expected premorbid lung weight was estimated from the subjects' height.[25] Recruitment and hyperinflation induced by any increase in airway pressure were computed as the absolute difference in *total volume* of the non-aerated or over-aerated compartment between 5 cmH_2O (or 10 cmH_2O in obese patients) and the higher airway pressure.[4,26,27] We used the hyperinflation-to-recruitment ratio to weigh the risks and benefits of higher airway pressure.

To be consistent with other studies on ARDS unrelated to COVID-19,[4,28] we also computed the recruited lung tissue as the difference in the non-aerated *tissue weight* between 5 cmH_2O (or 10 cmH_2O in obese patients) and the higher airway pressure and expressed it as a percentage of the lung weight with 5 cmH_2O (or 10 cmH_2O in obese patients). The tissue remaining non-aerated at 45 cmH_2O of airway pressure was considered consolidated.

The same methods were applied to ten equally spaced vertical levels forming each CT slice from the sternum to the vertebra. The pressure (super)imposed on each level was obtained as in references 2 and 29. In healthy subjects lying supine, the (maximal) superimposed pressure on the most dorsal level is 2.6±0.5 cmH_2O.[25]

Aiming to describe the response to a higher PEEP, we present all the results as if airway pressure had been increased throughout the study. Moreover, as we included only four obese patients, results of their PEEP trial are reported as obtained with 5, 10, and 15 (rather than 10, 15, and 20) cmH_2O of airway pressure, as for the other patients. Similarly, results of their lung CT are reported as obtained with 5 and 45 (rather than 10 and 45), or 5 and 15 (rather than 10 and 20), cmH_2O.

Please refer to the online data supplement for other details on methods.

<u>Statistical analysis</u>

Data are presented as the median (Q1-Q3) or proportion. They were analyzed with the Mann-Whitney rank-sum test, Wilcoxon signed rank-sum test, Fisher's exact test, Spearman's rank-order correlation, and Friedman's repeated-measures analysis of variance on ranks. Post-hoc comparisons were run with the Wilcoxon signed rank-sum test corrected with Bonferroni's method.

These analyses were done with Stata Statistical Software release 16 (Stata Corp. LLC; College Station, TX). A two-tailed p-value <0.05 was considered significant.

Results

We studied forty patients with COVID-19 on invasive mechanical ventilation. Their characteristics at ICU admission are reported in Tables E1 and E2. Thirty-three (82.5%) were males and seven (17.5%) females, with an age of 66 (59-72) years. Three (8%) had a history of chronic obstructive pulmonary disease (COPD), and four (10%) were obese. They were all transferred to the ICU for endotracheal intubation after 2 (1-5) days in the hospital. By that time, thirty-six (90%) had received some form of non-invasive ventilation. Initial C-reactive protein was 14 (8-17) mg/L. Fifteen (38%) died in the ICU.

The study was performed 1 (0-1) day after ICU admission. The lung function and morphology of all forty patients are described in Tables 1, E3 and E4. With 5 cmH_2O of PEEP, hypoxemia was mild (PaO_2:FiO_2 >200 mmHg) in five (13%), moderate (PaO_2:FiO_2 101-200 mmHg) in nineteen (47%), and severe (PaO_2:FiO_2 ≤100 mmHg) in sixteen (40%). The total lung volume was 2368 (2148-2624) ml: 21 (14-32)% in the non-aerated, 30 (25-36)% in the poorly-aerated, 44 (31-52)% in the normally-aerated, and 1.8 (0.3-5.9)% in the over-aerated compartment. The lung tissue weight was 1318 (1114-1633) g, 266 (143-570) g higher than expected. The lung gas volume was 999 (756-1309) ml. The superimposed pressure increased along the sterno-vertebral axis, up to 11 (10-13) cmH_2O. Accordingly, the non-aerated compartment was dorsal, and the over-aerated compartment was ventral (Figure E2).

Functional response to a higher PEEP

The individual changes in gas exchange and respiratory system mechanics with 5, 10, and 15 cmH_2O of PEEP are shown in Figure 1. The PaO_2:FiO_2 progressively increased while the compliance initially increased but then decreased. The $PaCO_2$ did not change. The mean arterial pressure slightly decreased, and the arteriovenous oxygen content difference increased (Table E5).

Overall, as PEEP was increased from 5 to 15 cmH_2O, oxygenation improved in thirty-six (90%) patients whilst compliance only in eleven (28%) and $PaCO_2$ only in fourteen (35%).

Morphological response to a higher PEEP

The quantitative analysis of lung CTs is shown in Tables 2 and 3 and in Figures 2, 3, and E2-E4.

From 5 to 45 cmH_2O of airway pressure, the total lung volume increased by 2131 (1516-2327) ml. The non-aerated compartment decreased by 351 (161-462) (range 79-771) ml, and the over-aerated increased by 465 (220-681) (range 5-1197) ml. On average, the over-aerated compartment increased by 1.7 (0.5-3.8) ml for a 1-ml decrease of the non-aerated compartment. Hyperinflation exceeded recruitment in twelve (60%) patients. The recruited tissue was 24 (14-35) (range 8-45)%, and the consolidated tissue 16 (9-23)% of the lung weight with 5 cmH_2O of PEEP.

From 5 to 15 cmH_2O of airway pressure, changes were similar but smaller. The total lung volume increased by 861 (751-1077) ml. The non-aerated compartment decreased by 168 (110-202) (range 50-585) ml, and the over-aerated increased by 121 (63-270) (range 8-524) ml. The over-aerated compartment increased by 1.1 (0.3-1.7) ml for a 1-ml decrease of the non-aerated compartment. Hyperinflation exceeded recruitment in eleven (55%) patients. The recruited tissue was 11 (9-14) (range 5-30)%.

With a higher airway pressure, recruitment occurred dorsally and hyperinflation ventrally (Figure E3).

The hyperinflation-to-recruitment ratio was associated with: (i) the maximal superimposed pressure (rho -0.862 and $p<0.001$ in patients studied at 5 and 45 cmH_2O; rho -0.838 and $p<0.001$ in those studied at 5 and 15 cmH_2O); (ii) the gas volume in the whole lung (rho 0.725 and $p<0.001$; rho 0.787 and $p<0.001$); (iii) the gas volume in the over-aerated compartment (rho 0.784 and $p<0.001$; rho 0.785 and $p<0.001$); and (iv) to some extent, compliance (rho 0.417 and $p=0.068$; rho 0.444 and $p=0.050$) (Table E6), all measured with 5 cmH_2O of PEEP. It was not associated with PaO_2:FiO_2 with 5 cmH_2O of PEEP (rho 0.216 and $p=0.361$; rho 0.390 and $p=0.090$). It was associated with the circulating C-reactive protein measured at ICU admission (rho -0.714 and $p<0.001$; rho -0.741 and $p<0.001$). To summarize, with a higher airway pressure, hyperinflation tended to exceed recruitment in patients with lower superimposed pressure, larger aeration and over-aeration with 5 cmH_2O of PEEP, somewhat higher compliance with 5 cmH_2O of PEEP, and less inflammation.

Discussion

The main findings of this study can be summarized as follows. In patients with early ARDS due to COVID-19, ventilated in the supine position, the response to a higher PEEP was variable. Arterial oxygenation usually improved but compliance and $PaCO_2$ frequently did not even if lung recruitment was large. This disagreement between changes in lung physiology and anatomy can be at least partly explained by the simultaneous occurrence of hyperinflation and overdistention.

The functional response to a higher PEEP suggested a *small* potential for recruitment. The arterial oxygenation quite constantly improved, but the compliance and the $PaCO_2$ did not. An isolated increase in arterial oxygenation does not necessarily signal large recruitment. Other mechanisms can play a role.[6,7] With a higher PEEP, the mean arterial pressure decreased, and the arteriovenous oxygen content difference increased as if the cardiac output had decreased. Arterial oxygenation may have thus increased because the non-aerated compartment became less perfused, independently of recruitment (see also Figure E5).[7] The decrease in compliance with a PEEP >10 cmH_2O also suggests little recruitment with net overdistention.[4-6] Other authors have hypothesized the same based on a very similar response to the PEEP trial in patients with early COVID-19.[13] However, those authors did not study the morphological response to a higher PEEP, so that they could not verify their hypothesis as we did.

Discovering with lung CT that patients with early COVID-19 have a very *large* potential for recruitment came as a surprise. In most,[14,18,30] but not all,[31] other studies on COVID-19, the potential for lung recruitment was small. Herein it was 24 (14-35)%, probably larger than reported in other pulmonary ARDS (16 [9-25]%)[28] (see also Figure E6). The reasons why our findings differ from previous ones may include our use of CT, the performance of a recruitment maneuver at the beginning of the study, enrollment of patients soon after their ICU admission, before any later decrease in lung recruitability.[14,32,33] In our study population, the alveolar collapse was almost fully reversible (see also Figure E7), and the residual consolidated tissue only 16 (9-22)% of the lung weight (in other pulmonary ARDS it is 28 [17-38]%).[28]

This disagreement between the functional and morphological response to a higher PEEP can be at least partly explained by simultaneous alveolar overdistention.[26,27] The net effect of PEEP depends on two opposite phenomena: non-aerated units regaining aeration versus already aerated units receiving more gas, up to the point of becoming over-stretched.[4,34,35] As PEEP was increased from 5 to 10 cmH_2O, the predominant response seemed to be dorsal recruitment, with less non-aerated tissue, better arterial oxygenation, and better compliance. When PEEP was increased to 15 cmH_2O, overdistention of the non-dependent lung regions possibly prevailed over any additional dorsal recruitment, with ventral overdistention at the CT and a sharp decline in compliance. Three aspects of our findings should be noted. First, CT is not ideal for measuring overdistention for the following reasons: hyperinflation can occur without overdistention, as in emphysema;[36] overdistention may develop without hyperinflation, at the interface between non-aerated and aerated units;[37] with ARDS, the decrease in CT density due to excessive inflation can be masked by the increased tissue mass.[2] With all these limitations, the decrease in compliance of the whole respiratory system (Table E5) and of the ventral lung levels (see Figure E2) suggest that overdistention developed in most patients. Second, end-expiratory lung CT underestimates end-inspiratory hyperinflation. Third, all of these changes occurred with seemingly protective ventilation. In all patients but one, including those with the largest PEEP-induced hyperinflation, driving and plateau airway pressures did not exceed 15 and 30 cmH_2O, not even with 15 cmH_2O of PEEP.[38]

Other factors may have contributed to the poor functional response to a higher PEEP in the face of large anatomical recruitment. On one side, the modest improvement in gas exchange could have been due to an abnormal distribution of pulmonary blood flow.[21-23] Arterial oxygenation will not increase much if the recruited alveoli are not well perfused. On the other side, compliance measured during tidal ventilation may not have increased with a higher PEEP because of cyclic recruitment (which increases compliance *per se*) with a lower PEEP.[39,40] The relationship between changes in lung aeration and compliance is complex; recruitment should not be estimated only from the latter.[41,42]

The superimposed pressure can be defined as the hydrostatic pressure acting on each lung level. With ARDS, it increases and contributes to the alveolar collapse.[2,29,43] PEEP restores aeration by counteracting the superimposed pressure.[43-45] Considering that in early ARDS due to COVID-19 the lung weight gain is modest (around 250 g), the airway pressure needed to recruit the lung (the opening pressure) and keep it open (PEEP) may be quite low. If so, a PEEP >10 cmH_2O will induce significant overdistention.[46]

Net hyperinflation was associated with C-reactive protein and compliance. With less inflammation, there will be less pulmonary edema, lower superimposed pressure, less alveolar collapse, larger lung gas volume, and higher compliance.[5] Changes in pulmonary perfusion will play a major role in the pathogenesis of hypoxemia.[21-23] Possibly, a lower PEEP will be appropriate. By contrast, with more inflammation and lower compliance, the superimposed pressure should be higher and the balance between hyperinflation and recruitment more favorable. A higher PEEP will be more indicated.

Some of the limitations of this study deserve a comment. First, the sample size was based on feasibility limitations due to the ongoing pandemic. Some subgroup analyses were probably underpowered. Second, during the first wave of the pandemic, we could not enroll all consecutive eligible patients, which may have been a source of bias.

Third, we did not include a control group to compare patients with COVID-19 with those with other ARDS, especially for the frequency and severity of overdistention. It may be worth noting that in our study, increasing PEEP from 5 to 15 cmH_2O enlarged the over-aerated compartment in all patients, including nineteen with no history of COPD (on average by 118 [53-253] ml). By contrast, in a previous study on thirty-two patients with ARDS of other origins, increasing PEEP from 0 to 15 cmH_2O did the same in only fourteen (44%), and only in eight (31%) of those with no history of COPD (on average by 25 [19-28] ml).[27] Fourth, lung CTs were not taken at 10 cmH_2O of PEEP. Our model, with predominant recruitment below that threshold and hyperinflation above it, has to be validated. Fifth, the lung phenotype in COVID-19 changes over time,[47] so that our findings may not be valid for later stages of the disease.[14,32,33]

Clinical implications

International guidelines suggest using a higher PEEP to relieve moderate-to-severe hypoxemia due to COVID-19.[11] Accordingly, among 3988 patients admitted to an Intensive Care Unit in our region (Lombardy, Italy), half were ventilated with a PEEP >12 cmH_2O, and one fourth with a PEEP >15 cmH_2O.[48] In retrospect, PEEP on day 1 of ICU admission was an independent risk factor of death: for any 1-cmH_2O increase, mortality increased by 4%.[48]

We did not study the impact of a higher or lower PEEP on clinically relevant outcomes, such as survival or duration of mechanical ventilation. Therefore, our findings do not provide any evidence on how to set the ventilation in patients with COVID-19. Even so, they suggest that the response to a higher PEEP can be hardly predictable; and that some patients might benefit from a lower PEEP, even if their ARDS is moderate or severe. Considering changes in gas exchange, respiratory system mechanics, and lung aeration (measured with the CT or other technique) as a whole may help the clinicians to set PEEP according to the characteristics of every single patient.

In conclusion, in this group of patients with early COVID-19, ventilated in the supine position, the response to a higher PEEP was variable and usually less favorable than expected for the severity of hypoxemia and the potential for lung recruitment. Signs of hyperinflation and overdistention were common.

Acknowledgments

AP takes responsibility for the content of the manuscript, including the data and analysis. AP contributed to the conception and design of the study, analysis, and interpretation of the data and wrote the manuscript. AS contributed to the conception and design of the study, collection, analysis, and interpretation of the data, and revised the manuscript. FP, CC, MCr contributed to the collection, analysis, and interpretation of the data and revised the manuscript. MF, GEI, LC, EL contributed to the collection of the data and revised the manuscript. GP contributed to the analysis of the data and revised the manuscript. PC, AA, and MCe contributed to the conception of the study, interpretation of the data, and revised the manuscript. All authors have read and approved this final version of the manuscript.

We are grateful to all nurses, physicians, and other healthcare professionals who helped us perform this study. The following colleagues contributed to the collection, analysis, or interpretation of the data: Francesca Collino, M.D., Elena Costantini, M.D., Francesca Dalla Corte, M.D., Maxim Neganov, M.D., and Valerio Rendiniello, N.P. (Department of Anesthesia and Intensive Care Units, Humanitas Clinical and Research Center – IRCCS, Rozzano, Milan, Italy); Nicolò Martinetti, M.D., and Luca Pugliese, M.D. (Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy).

Take Home Point:

Study Question: What is the response to a higher PEEP in mechanically ventilated patients with early ARDS due to COVID-19?

Results: When PEEP is increased from 5 to 15 cmH<sub>2<sub>O, oxygenation usually improves but compliance and the arterial carbon dioxide tension do not. Lung computed tomography shows that when the airway pressure is increased from 5 up to 45 cmH<sub>2<sub>O, recruitment is large but hyperinflation can be even larger.

Interpretation: In patients with early ARDS due to COVID-19, a higher PEEP can induce net hyperinflation with overdistention.

References

1) Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2(7511):319-323.
2) Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med*. 2001;164(9):1701-1711.
3) Gattinoni L, Pesenti A, Bombino M, et al. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. *Anesthesiology*. 1988;69(6):824-832.
4) Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354(17):1775-1786.
5) Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis*. 1987;136(3):730-736.
6) Caironi P, Gattinoni L. How to monitor lung recruitment in patients with acute lung injury. *Curr Opin Crit Care*. 2007;13(3):338-343.
7) Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. *Chest*. 1980;77(5):636-642.
8) Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873.

9) Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-755.

10) Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263.

11) Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46(5):854-887.

12) Chauvelot L, Bitker L, Dhelft F, et al. Quantitative-analysis of computed tomography in COVID-19 and non COVID-19 ARDS patients: A case-control study. *J Crit Care*. 2020;60:169-176.

13) Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med*. 2020;46(12):2187-2196.

14) Ball L, Robba C, Maiello L, et al. Computed tomography assessment of PEEP-induced alveolar recruitment in patients with severe COVID-19 pneumonia. *Crit Care*. 2021;25(1):81.

15) Beloncle FM, Pavlovsky B, Desprez C, et al. Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. *Ann Intensive Care* 2020;10(1):55.

16) Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. *Crit Care*. 2020;24(1):529.

17) Mauri T, Spinelli E, Scotti E, et al. Potential for lung recruitment and ventilation-perfusion mismatch in patients with the acute respiratory distress syndrome from Coronavirus Disease 2019. *Crit Care Med*. 2020;48(8):1129-1134.

18) Pan C, Chen L, Lu C, et al. Lung Recruitability in COVID-19-associated acute respiratory distress syndrome: a single-center observational study. *Am J Respir Crit Care Med*. 2020;201(10):1294-1297.

19) Perier F, Tuffet S, Maraffi T, et al. Effect of positive end-expiratory pressure and proning on ventilation and perfusion in COVID-19 acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;202(12):1713-1717.

20) Grasso S, Mirabella L, Murgolo F, et al. Effects of positive end-expiratory pressure in "high compliance" severe acute respiratory syndrome coronavirus 2 acute respiratory distress syndrome. *Crit Care Med*. 2020;48(12):e1332-e1336.

21) Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med*. 2020;8(12):1201-1208.

22) Herrmann J, Mori V, Bates JHT, Suki B. Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia. *Nat Commun*. 2020;11(1):4883.

23) Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med*. 2020;202(5):690-699.

24) ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.

25) Cressoni M, Gallazzi E, Chiurazzi C, et al. Limits of normality of quantitative thoracic CT analysis. *Crit Care*. 2013;17(3):R93.

26) Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome. *Intensive Care Med*. 2000;26(9):1215-1227.

27) Nieszkowska A, Lu Q, Vieira S, Elman M, Fetita C, Rouby JJ. Incidence and regional distribution of lung overinflation during mechanical ventilation with positive end-expiratory pressure. *Crit Care Med*. 2004;32(7):1496-1503.

28) Coppola S, Froio S, Marino A, et al. Respiratory mechanics, lung recruitability, and gas exchange in pulmonary and extrapulmonary acute respiratory distress syndrome. *Crit Care Med*. 2019;47(6):792-799.

29) Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(1):8-13.

30) Haudebourg AF, Perier F, Tuffet S, et al. Respiratory mechanics of COVID-19- versus non-COVID-19-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;202(2):287-290.

31) Smit MR, Beenen LFM, Valk CMA, et al. Assessment of lung reaeration at 2 levels of positive end-expiratory pressure in patients with early and late COVID-19-related acute respiratory distress syndrome. *J Thorac Imaging*. 2021;36(5):286-293.

32) Kummer R, Shapiro R, Marini J, Huelster J, Leatherman J. Paradoxically improved respiratory compliance with abdominal compression in COVID-19 ARDS. *Chest*. In press. doi: 10.1016/j.chest.2021.05.012.

33) Rezoagli E, Bastia L, Grassi A, et al: Paradoxical effect of chest wall compression on respiratory system compliance: a multicenter case series of patients with ARDS, with multimodal assessment. *Chest*. In press. doi: 10.1016/j.chest.2021.05.057.

34) Dambrosio M, Roupie E, Mollet JJ, et al. Effects of positive end-expiratory pressure and different tidal volumes on alveolar recruitment and hyperinflation. *Anesthesiology*. 1997;87(3):495-503.

35) Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002;165(8):1182-1186.

36) Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med*. 2001;164(1):131-140.

37) Cressoni M, Cadringher P, Chiurazzi C, et al. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2014;189(2):149-158.

38) Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2007;175(2):160-166.

39) Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L. Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *Am J Respir Crit Care Med*. 1999;159(4 Pt 1):1172-1178.

40) Chen L, Del Sorbo L, Grieco DL, et al. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome. A clinical trial. *Am J Respir Crit Care Med*. 2020;201(2):178-187.

41) Chiumello D, Marino A, Brioni M, et al. Lung recruitment assessed by respiratory mechanics and computed tomography in patients with acute respiratory distress syndrome. What is the relationship? *Am J Respir Crit Care Med*. 2016;193(11):1254-1263.

42) Amato MB, Santiago RR. The recruitability paradox. *Am J Respir Crit Care Med*. 2016;193(11):1192-1195.

43) Cressoni M, Chiumello D, Carlesso E, et al. Compressive forces and computed tomography-derived positive end-expiratory pressure in acute respiratory distress syndrome. *Anesthesiology*. 2014;121(3):572-581.

44) Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA*. 1993;269(16):2122-2127.

45) Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;151(6):1807-1814.

46) Protti A, Greco M, Filippini M, et al. Barotrauma in mechanically ventilated patients with Coronavirus disease 2019: a survey of 38 hospitals in Lombardy, Italy. *Minerva Anestesiol*. 2021;87(2):193-198.

47) Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425-434.

48) Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345-1355.

Figure 1. The functional response to a higher PEEP.

Gas exchange and respiratory system compliance were measured with 5, 10, and 15 cmH_2O of positive end-expiratory pressure (PEEP) while other ventilatory settings were kept constant (the so-called "PEEP trial"). Herein we show individual data recorded with the three different levels of PEEP and the group median values (red bars). PaO_2: arterial tension of oxygen. FiO_2: inspiratory fraction of oxygen. The compliance was the ratio of tidal volume to driving airway pressure, the difference between plateau airway pressure and total PEEP. $PaCO_2$: arterial tension of carbon dioxide. P-values refer to the overall Friedman's test (above), and the post-hoc Wilcoxon signed rank-sum test, corrected with Bonferroni's method (below).

Figure 2. Lung volume distribution of computed tomography (CT) densities at 5, 15, or 45 cmH_2O of airway pressure.

Forty patients with COVID-19 underwent a lung CT at 5 cmH_2O of airway pressure. Twenty of them had a second CT taken at 15 cmH_2O, and the other twenty at 45 cmH_2O of airway pressure. Herein we show the individual and median distributions of lung volume (tissue and gas) as a function of the physical densities measured in Hounsfield units (HU). With a higher pressure, volumes with density above -100 HU (non-aerated) decreased, as for alveolar recruitment, while those with density from -500 to -900 (normally-aerated) increased, as for better aeration. Volumes with a density below -900 HU (over-aerated) simultaneously increased, as for hyperinflation. Volumes with a density from -800 to -900 HU, which can become over-aerated after tidal inflation,[26] increased as well. The over-aerated compartment in some patients at

5 or 15 cmH_2O was larger than in others at 45 cmH_2O of airway pressure (see also Figure E4).

Figure 3. Color-coded analysis of lung computed tomography (CT) data.

Representative CT images taken at the level of carina at 5 and 45 cmH_2O of airway pressure from three patients with COVID-19 and very different degrees of recruitment and hyperinflation. Upper panels: original lung CT images, with aeration shown on a continuous grayscale. Lower panels: using an automated encoding system, we attributed a specific color to the non-aerated, poorly-aerated, normally-aerated, and over-aerated compartments. Left panels: recruitment 457 ml and hyperinflation 5 ml. With 5 cmH_2O of PEEP, maximal superimposed pressure was 13.4 cmH_2O; compliance 27 ml/cmH_2O; PaO_2:FiO_2 90 mmHg. C-reactive protein at ICU admission was 20 mg/L. Central panels: recruitment 347 ml and hyperinflation 661 ml. Maximal superimposed pressure 11.5 cmH_2O; compliance 44 ml/cmH_2O; PaO_2:FiO_2 104 mmHg. C-reactive protein 10 mg/L. Right panels: recruitment 160 ml and hyperinflation 993 ml. Maximal superimposed pressure 9.4 cmH_2O; compliance 60 ml/cmH_2O; PaO_2:FiO_2 80 mmHg. C-reactive protein 1 mg/L. None of these patients had a history of COPD or was obese.

Table 1. Characteristics of forty patients with COVID-19, the day of the study and with 5 cmH_2O of PEEP.

Variable		
N		40
Ventilatory setting		
Tidal volume (ml)		420 (385-445)
Tidal volume (ml/kg of PBW)		6.1 (5.9-6.7)
Respiratory rate (bpm)		20 (18-22)
FiO_2 (%)		60 (55-95)
Minute ventilation (L/min)		8.3 (7.3-9.9)
Respiratory system mechanics		
Plateau airway pressure (cmH_2O)		15 (14-16)
Driving airway pressure (cmH_2O)		9 (8-10)
Compliance (ml/cmH_2O)		45 (42-51)
Gas exchange		
Arterial pH		7.39 (7.34-7.43)
$PaCO_2$ (mmHg)		47 (40-51)
PaO_2 (mmHg)		78 (66-90)
PaO_2/FiO_2 (mmHg)		112 (84-154)
Lung tissue and gas distribution		
Total lung	Tissue (g)	1318 (1114-1633)
	Gas (ml)	999 (756-1309)
Non-aerated	Tissue (g)	526 (384-743)
	Gas (ml)	5 (0-10)
Poorly-aerated	Tissue (g)	516 (406-601)
	Gas (ml)	216 (167-244)
Normally-aerated	Tissue (g)	286 (193-382)
	Gas (ml)	713 (507-959)
Over-aerated	Tissue (g)	3 (1-7)
	Gas (ml)	40 (8-129)

All data refer to the time of the study. Respiratory system mechanics and gas exchange were measured with 5 cmH_2O of PEEP. Other ventilator settings were at the discretion of the attending physicians. Lung CTs were taken in static conditions during an end-expiratory pause with 5 cmH_2O of PEEP. PBW: predicted body weight. FiO_2: inspiratory fraction of oxygen. $PaCO_2$: arterial tension of carbon dioxide. PaO_2: arterial tension of oxygen. The driving airway pressure was the difference between the plateau airway pressure and total PEEP measured with a 5-second end-inspiratory and end-expiratory pause. The compliance was the ratio of the tidal volume to the driving airway pressure. Data are reported as median (Q1-Q3). If the non-aerated compartment had a density >0 HU (i.e., higher than the density of water), the gas volume (in ml) was considered zero.

Table 2. Lung tissue and gas distribution with 5 and 45 cmH_2O of airway pressure.

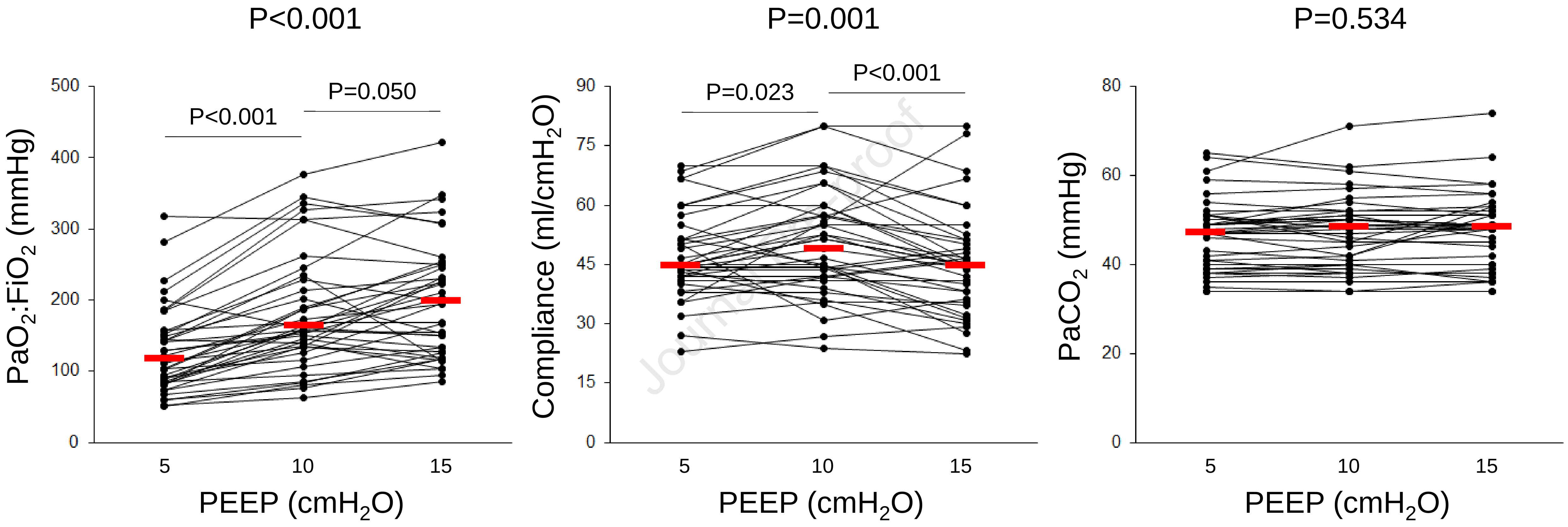
Variable		**Quantitative analysis of lung CT**		**P-value**
Airway pressure (cmH_2O)		5	45	
N		20	20	
Total lung	Tissue (g)	1336 (1112-1586)	1439 (1157-1575)	0.062
	Gas (ml)	950 (577-1230)	2905 (2410-3345)	<0.001
Non-aerated	Tissue (g)	555 (404-742)	197 (115-307)	<0.001
	Gas (ml)	3 (0-10)	0 (0-2)	0.008
Poorly-aerated	Tissue (g)	502 (364-601)	378 (313-498)	0.011
	Gas (ml)	192 (160-256)	199 (164-274)	0.852
Normally-aerated	Tissue (g)	255 (156-382)	777 (598-882)	<0.001
	Gas (ml)	658 (356-922)	2288 (1474-2484)	<0.001
Over-aerated	Tissue (g)	3 (0-7)	31 (18-45)	<0.001
	Gas (ml)	46 (6-131)	476 (217-766)	<0.001

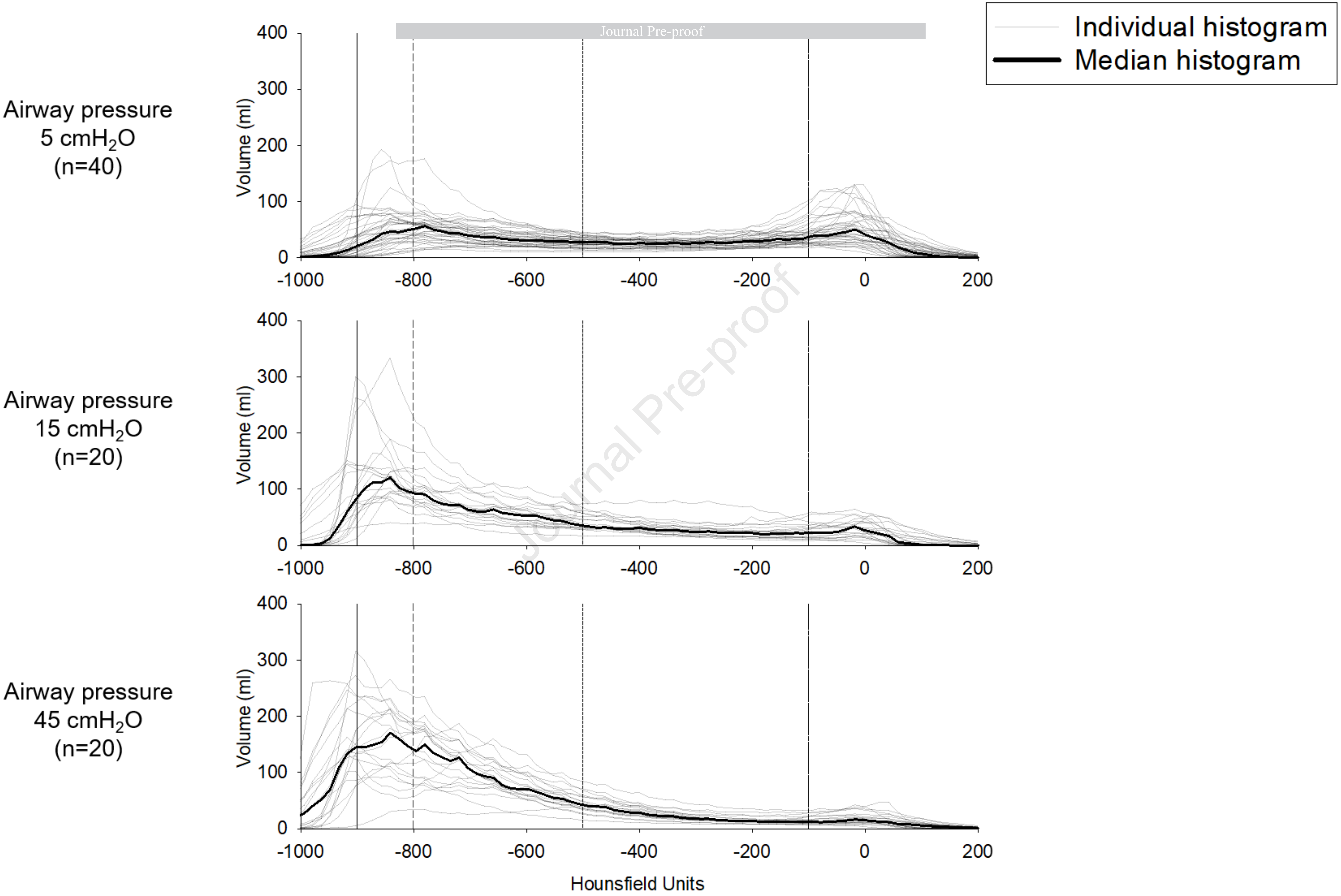
Twenty patients underwent a lung CT at 5 and 45 cmH_2O of airway pressure. Herein we compare the distribution of tissue and gas in their whole lungs and in their four compartments at these two airway pressures. Data are reported as median (Q1-Q3). P-value refers to the Wilcoxon signed rank-sum test. If the non-aerated compartment had a density >0 HU (i.e., higher than the density of water), the gas volume was considered zero.

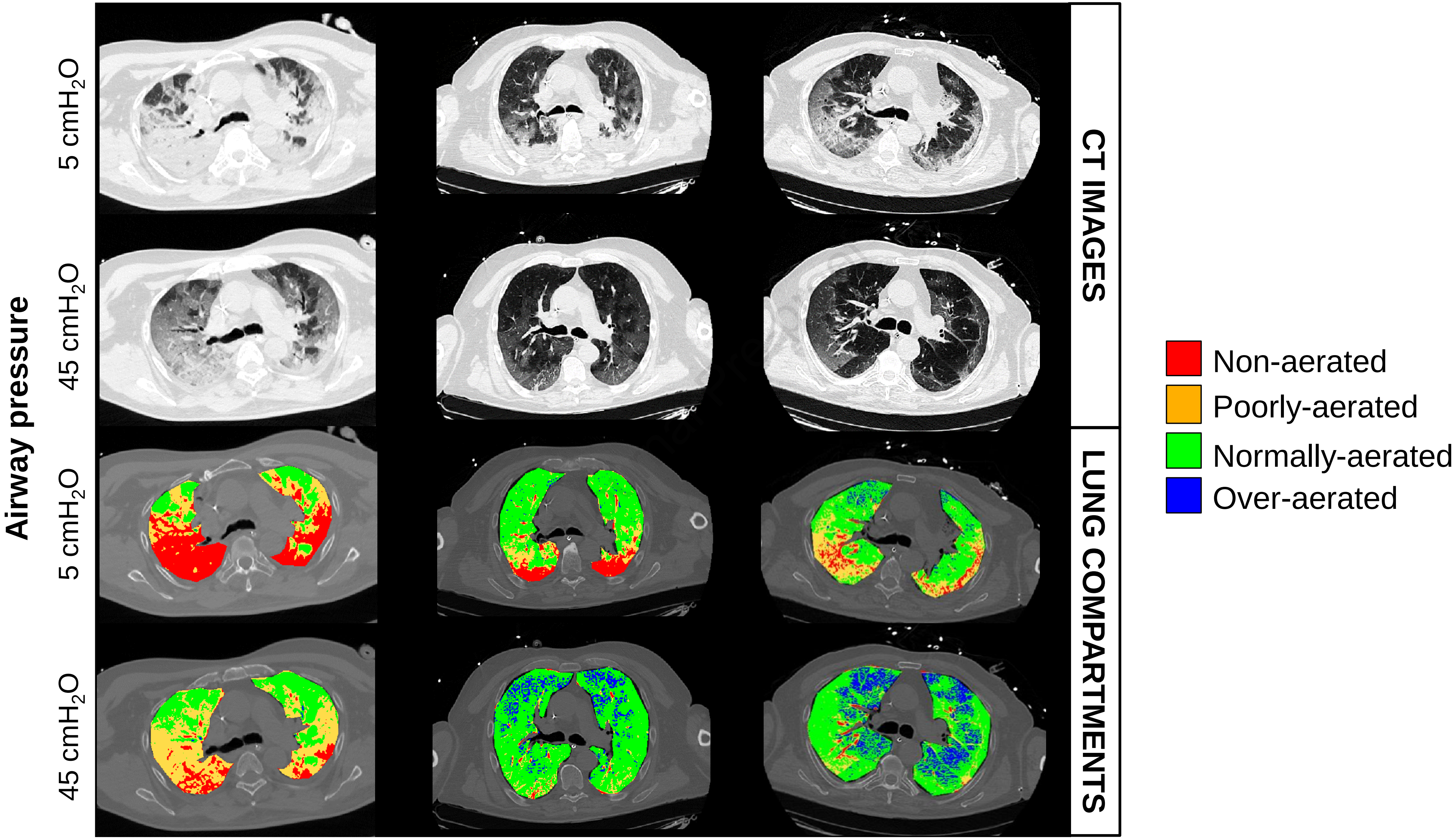
Table 3. Lung tissue and gas distribution with 5 and 15 cmH_2O of airway pressure.

Variable		**Quantitative analysis of lung CT**		**P-value**
Airway pressure (cmH_2O)		5	15	
N		20	20	
Total lung	Tissue (g)	1301 (1157-1658)	1331 (1172-1696)	0.003
	Gas (ml)	999 (913-1393)	1943 (1683-2322)	<0.001
Non-aerated	Tissue (g)	475 (311-754)	301 (140-444)	<0.001
	Gas (ml)	5 (0-10)	2 (0-6)	0.002
Poorly-aerated	Tissue (g)	517 (438-596)	479 (345-601)	0.794
	Gas (ml)	219 (190-233)	220 (174-293)	0.014
Normally-aerated	Tissue (g)	305 (255-388)	517 (471-598)	<0.001
	Gas (ml)	722 (642-989)	1414 (1225-1749)	<0.001
Over-aerated	Tissue (g)	1 (1-7)	10 (6-26)	<0.001
	Gas (ml)	16 (8-102)	130 (70-324)	<0.001

Twenty patients underwent a lung CT at 5 and 15 cmH_2O of airway pressure. Herein we compare the distribution of tissue and gas in their whole lungs and in their four compartments at these two airway pressures. Data are reported as median (Q1-Q3). P-value refers to the Wilcoxon signed rank-sum test. If the non-aerated compartment had a density >0 HU (i.e., higher than the density of water), the gas volume was considered zero.


P<0.001
P=0.001
P=0.534
PaO2:FiO2 (mmHg)
P<0.001
P=0.050
500
400
300
200
100
0
5
10
15
PEEP (cmH2O)
Compliance (ml/cmH2O)
P=0.023
P<0.001
90
75
60
45
30
15
0
5
10
15
PEEP (cmH2O)
PaCO2 (mmHg)
80
60
40
20
0
5
10
15
PEEP (cmH2O)


Individual histogram
Median histogram
Airway pressure
5 cmH2O
(n=40)
Airway pressure
15 cmH2O
(n=20)
Airway pressure
45 cmH2O
(n=20)
Volume (ml)
Hounsfield Units
400
300
200
100
0
-1000
-800
-600
-400
-200
0
200


Airway pressure
5 cmH2O
45 cmH2O
5 cmH2O
45 cmH2O
CT IMAGES
LUNG COMPARTMENTS
Non-aerated
Poorly-aerated
Normally-aerated
Over-aerated

List of abbreviations

- ARDS: acute respiratory distress syndrome
- COPD: chronic obstructive pulmonary disease
- COVID-19: coronavirus disease 2019
- CT: computed tomography
- FiO_2: fraction of inspired oxygen
- ICU: intensive care unit
- $PaCO_2$: arterial carbon dioxide tension
- PaO_2: arterial oxygen tension
- PEEP: positive end-expiratory pressure
- Q1: first quartile
- Q3: third quartile